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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/993,564	12/18/1997	STUART A. NEWMAN	45010-00601	5286

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EXAMINER
CROUCH, DEBORAH

ART UNIT	PAPER NUMBER
1632	23

DATE MAILED: 01/29/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application N .	Applicant(s)	
	08/993,564	NEWMAN, STUART A.	
	Examiner	Art Unit	
	Deborah Crouch, Ph.D.	1632	

-- The MAILING DATE f this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *07 February 2001 and 19 June 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,4,6,7,10,13,28,30,31,33,34,38-43,50,53,55 and 59-92* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,4,6,7,10,13,28,30,31,33,34,38-43,50,53,55 and 59-92* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Applicant's Amendment and Response filed February 7, 2001 (Paper No. 20) has been entered. Also, applicant's response filed June 19, 2002 (Paper No. 21) has been entered. However, applicant's arguments are not persuasive. Claims 2, 5, 16, 29, 32, 44-48, and 56-58 have been canceled, claims 1, 3, 4, 6, 7, 10, 13, 28, 30, 31, 33, 34, 39-43, 53, 59, and 70 have been amended, and claims 72-92 have been added. Claims 1, 3, 4, 6, 7, 10, 13, 28, 30, 31, 33, 34, 38-43, 50, 53, 55, and 59-92 are pending and are under current examination.

Applicant is advised that claims 2, 5, 16, 29, 32, 44-48 and 56-58, discussed in the response filed June 19, 2002, were canceled in the response of February 7, 2001. Thus, arguments regarding these claims are moot, and are not addressed in this office action.

The PTO 1449 filed as an attachment to the response of February 7, 2001 fails to comply with the provisions of 37 CFR § 1.97, 1.98 and MPEP § 609. Applicant has not complied with 37 CFR § 1.97(c) by filing the fee set forth in 37 CFR § 1.17(p), nor a statement under 37 CFR § 1.97 (e). Furthermore, the provisions of 37 CFR § 1.98 have not been fulfilled, as copies of the references have not been submitted. In addition, the information disclosure statement, filed June 19, 2002, fails to comply with 37 CFR § 1.97(c) because it lacks a fee as specified in 37 CFR § 1.17(p), or a statement as specified in 37 CFR § 1.97(e). These information disclosure statements have been placed in the application file, but the information referred to therein has not been considered, nor made of record. For guidance regarding filing information disclosure statements, applicant should refer to MPEP 609.

The Examiner and art unit of record have changed. The Examiner and art unit of record is now Deborah Crouch of art unit 1632.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

Applicant's Amendment and Response filed February 7, 2001 (Paper No. 20) has been entered. Also, applicant's response filed June 19, 2002 (Paper No. 21) has been entered. However, applicant's arguments are not persuasive. Claims 2, 5, 16, 29, 32, 44-48, and 56-58 have been canceled, claims 1, 3, 4, 6, 7, 10, 13, 28, 30, 31, 33, 34, 39-43, 53, 59, and 70 have been amended, and claims 72-92 have been added. Claims 1, 3, 4, 6, 7, 10, 13, 28, 30, 31, 33, 34, 38-43, 50, 53, 55, and 59-92 are pending and are under current examination.

Applicant is advised that claims 2, 5, 16, 29, 32, 44-48 and 56-58, discussed in the response filed June 19, 2002, were canceled in the response of February 7, 2001. Thus, arguments regarding these claims are moot, and are not addressed in this office action.

The PTO 1449 filed as an attachment to the response of February 7, 2001 fails to comply with the provisions of 37 CFR § 1.97, 1.98 and MPEP § 609. Applicant has not complied with 37 CFR § 1.97(c) by filing the fee set forth in 37 CFR § 1.17(p), nor a statement under 37 CFR § 1.97 (e). Furthermore, the provisions of 37 CFR § 1.98 have not been fulfilled, as copies of the references have not been submitted. This IDS has been placed in the application file, but the information referred to therein has not been considered, nor made of record. In addition, the information disclosure statement, filed June 19, 2002, fails to comply with 37 CFR § 1.97(c) because it lacks a fee as specified in 37 CFR § 1.17(p), or a statement as specified in 37 CFR § 1.97(e). The information referred to therein has been considered and made of record only concerning those references specifically supplied and argued by applicant in the response. For guidance regarding filing information disclosure statements, applicant should refer to MPEP 609.

The Examiner and art unit of record have changed. The Examiner and art unit of record is now Deborah Crouch of art unit 1632.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The prior rejection of claim 16 as being anticipated by or, in the alternative, as being obvious over humans or non-human primates as found in nature, is moot in view of Applicant's cancellation of the claim.

The prior rejection of claims 28 and 32-34 under 35 U.S.C. 102(b) as being anticipated by Pixely et al. is withdrawn in view of the amendment to claim 28 limiting the cells from the one or more second animal species to non-human primate species.

Claims 10 and 68 stand rejected under 35 U.S.C. 102(b) as being anticipated by ATCC entries HTB 157, 158, and 160 for reasons set forth in the office action mailed August 7, 2000 in paper no. 17. It is noted that ATCC entries HTB 157, 158 and 160 are isolated human embryonic and fetal cells.

Claims 10, 50, and 68 stand rejected under 35 U.S.C. 102(b) as being anticipated by ATCC entry CRL-2378, designated MA-104 for reasons set forth in the office action August 7, 2000 in paper no. 17. It is noted that ATCC entry CRL-2378 is a Rhesus monkey embryonic kidney cell line.

Applicant argues that amendment to claim 10 requiring the cell line to be "immunologically tolerant to said cells from said first and said one or more second animals species" overcomes the rejection over ATCC entry CRL-2378.

Applicant argues the rejections over ATCC entries together.

Applicant argues that cells derived from chimeras are known to differ in immunological properties from equivalent cells in non-chimeric animals, and thus one of ordinary skill in the art would expect that this difference would likely pertain to cell lines derived from chimeras. Applicant argues that the amendment to claim 10 requiring the cell line to be "immunologically tolerant to said cells from said first

and said one or more second animals species" overcomes the rejection. Applicant argues that chimeras produced according to the specification would be expected to be immunologically unprecedented in that they would likely be tolerant to grafts from both human and the nonhuman species used, but not from other species. Applicant argues that Gustafson showed that sheep-goat chimeras did not exhibit an immune response to cells or grafts from sheep or goat siblings. Applicant argues that the acceptance of cells and grafts by a sheep-goat chimera from a sheep or goat sibling is because of the induction of protective genes in the chimeric animal's endothelium during development. Further, applicant argues that the athymic nude mouse accepts the grafts of other species because the mouse's immune system is entirely compromised. These arguments are not persuasive.

The claims are to a cell line isolated from a chimeric embryo, where the cells from the human component of the chimera are embryonic cells, blastomere cells, blastocyst cells, undifferentiated immortal cells, pluripotent cells and totipotent cells, where the cells from the nonhuman primate component are embryonic cells, embryonic stem cells, blastomere cells, blastocyst cells, undifferentiated immortal cells, pluripotent cells and totipotent cells, and wherein the cell line is immunologically tolerant to said cells from said first and said one or more animal species. However, at no place in the specification is there a definition or discussion as what applicant intends by the term "immunologically tolerant." The question therefore arises, does immunologically tolerant mean that the host permanently accepts the graft, or does the term mean that the graft is tolerated more than a complement-mediated rejection? It is maintained that any human or nonhuman primate cell of the claims would be, at a minimum, immunologically tolerated by either a human or nonhuman primate host, for some period of time greater than the immediate graft rejection observed in complement mediated graft rejection. Thus, the human embryonic cells of ATCC entries HTB 157, 158 and 160, and CRL-2378 would exhibit immunological tolerance when implanted into a human, or when implanted into nonhuman primates. There is no requirement that the degree of "immunological tolerance" be sufficient for any effect to be observed, or

that the graft last any particular length of time. Thus, the term "immunological tolerance" has been given the broadest reasonable interpretation. Let there be no confusion as to what the examiner understands applicant's argument to be: that the cells of the chimeric embryo would exhibit tolerance when either implanted or grafted into, or exposed to cells, from either the human or the nonhuman primate that donated cells for the construction of the chimeric embryo. The problem with applicant's argument and amendment lies in the lack of a definition of "immunologically tolerant." It is argued that the human embryonic cells of the cited ATCC entries would be tolerant to some degree in either a human or a nonhuman primate. Applicant is invited to provide a citation in the specification that defines "immunologically tolerant." Furthermore, neither the process of gaining recognition of self during development, nor the immune system defect of the nude mouse is seen as germane to the argument. Neither of these phenomena addresses the definition of "immunologically tolerant."

Additionally, the claims are to a cell line made by a process. Thus, as the cells in the prior art have the same characteristics of the cells of the claim, the ATCC entries would anticipate the claimed cell lines. One in possession of the claimed cells lines would be unable to distinguish them from those cell lines of the ATCC entries. Applicant is referred to MPEP 2113 for a discussion of product by process claims.

Claims 13, 66, 67, and 69-71 stand rejected under 35 U.S.C. 102(b) as being anticipated by Starzl et al. for reasons set forth in the office action mailed August 7, 2000 in paper no. 17.

Applicant argues that the claims have been amended to more accurately describe the present invention, including embryonic cell types and tolerance of the claimed chimeric animal to cells from the first and one or more second animal species. Applicant argues that the human-animal chimeras of Starzl are different from those claimed since Starzl discloses chimeras where adult tissue of one species colonizes with adult tissues of another species, rather than the developmental cooperation of early embryonic cell types of different species. Applicant argues that experimental chimeras, such as geeps, had phenotypic and morphological properties of both species, as well has histological identifiable cells of

numerous different types from both species. Applicant argues that the patients of Starzl who had received baboon organs in transplantation proceedings, were not reported to exhibit any morphological or phenotypic similarities to baboons or chimpanzees, nor did they exhibit any tissue level chimerism, other that that due to leukocyte transfusion from donor species.

Applicant is arguing limitations not in the claims. The claims are drawn to a chimeric animal, where the animal is immunologically tolerant to cells from a human and nonhuman primate. The remainder of the claims is to how the chimeric animal was produced. In a product by process, the product is patentable when previously made by another process only if the new process imbues a patentably distinct characteristic. This type of characteristic is not present for the chimeric animal product. Thus, the humans disclosed in Starzl are chimeric and produced by organ transplantation where the organs were donated by baboons or chimpanzees. There is no requirement in the claims that there be tissue level chimerism, and by corollary, no exclusion of the situation where an organ is made up entirely of tissue from one of the animals used to produce the claimed chimera. The claims read equally on the situation of tissue level chimerism and tissue level same species. Further, the chimeric animal would be tolerant to some degree of cells from either the human donor cells or the nonhuman primate donor cells. As discussed above, the specification provides no guidance or definition as to the meaning of the term "immunologically tolerant." Without guidance or definition, the term is given the broadest possible interpretation, i.e., that rejection is not so immediate that the implant cell, tissue or organ is not instantly rejected. Further, the presence of baboon and chimpanzee leukocytes is a form of mixed tissue chimerism that is not excluded by the claim.

Applicant makes reference to the Herbert declaration (Exhibit A) in support of their arguments regarding the rejection over Starzl. However, applicant did not point to any particular sections of the declaration where relevant statements were presented, and no reference to Starzl in the declaration could be found. Thus, the Herbert declaration is not persuasive.

Applicant's addition of new claims 72-92 necessitated the new ground(s) of rejection as follows:

Claims 83 and 86-90 are rejected under 35 U.S.C. 102(b) as being anticipated by Starzl et al. (*supra*).

Claims 83 and 86-90 are directed to a product, namely, a chimeric animal, wherein said chimeric animal contains cells derived from a human and cells derived from one or more non-human primates in two or more organs. Please note that limitations in the claims drawn to the process of making the chimeric embryo from which the animal "originated" and the intended use of the chimeric animal are not given patentable weight in the determination of anticipation. Patentability of a product-by-process claim is determined by the novelty and nonobviousness of the claimed product itself; product-by-process claims are not limited to the manipulations of the recited steps, but only to the structure implied by the steps. *In re Thorpe*, 227 USPQ 964 (Fed. Cir. 1985). Furthermore, with respect to claims 86-90, recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art.

Starzl et al. discuss generating chimerism in humans, and specifically report on humans which are genetic composites comprising baboon kidneys or livers. See pages 214, 215, and 219. Starzl et al. specifically discuss that the baboon donor leukocytes from the transplanted organ migrate to all tissues of the human. See page 219, 3rd paragraph. Thus, the chimeric humans of Starzl et al. meet all the limitations of the claims.

Further, the specification does not define any human cell – nonhuman primate cell composition for the chimera. Thus the claims encompass a human with one nonhuman primate cell or a nonhuman primate with one human cell. The teachings of Starzl clear teach humans with primate cells, and by applicant's definition these humans are chimeras.

Accordingly, Starzl et al. anticipate claims 83 and 86-90.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The prior rejection of claim 16 as being anticipated by or, in the alternative, under 35 U.S.C. 103(a) as being obvious over humans or non-human primates as found in nature, is moot in view of Applicant's cancellation of the claim. Claims 1, 28, 33, 34, 38-43, and 59-65 stand and claims 72-76, 79, 81-82, 91, and 92 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gustafson et al for the reasons advanced on pages 12-13 of the prior Office action mailed 8/7/00, Paper No.17.

Applicant argues that the claims have been amended to indicate that the embryonic cells used to form the chimeric embryo must cooperate, not merely aggregate, to form a viable embryo. See pages 23-25 of Paper No. 20. However, this concept, that the embryonic cells of said first and second species remain attached to one another and cooperate in the formation of a further developing embryo, is not taught in the specification. Therefore, the meets and bounds of the claim are not clear. Moreover, it is not clear as to whether a mere aggregate, a mixture of embryonic cells of the said first and second species, is encompassed by the instant claims.

The prior rejection under 35 U.S.C. 103 is maintained for the reasons advanced on pages 12-13 of the prior Office action (Paper No. 17) because the claims, given their broadest reasonable interpretation, still embody the starting point of the development of an embryo, *i.e.*, aggregation of the embryonic cells, and not necessarily any point beyond aggregation. (See 35 U.S.C. § 112, second paragraph rejection, infra.)

Applicant argues that one of ordinary skill in the art would not have been motivated to apply the teachings of Gustafson to a chimeric embryo comprising human cells. Applicant argues that to shift from the teaching of Gustafson to primates represents a major displacement from the area of teaching of Gustafson. However, though Gustafson utilized animals that were agriculturally desirable, the reference was published in the Journal of Reproduction and Fertility, which is not a journal merely for agriculture, but instead focuses on reproductive biology. Applicant argues that there is a teaching away for social

and cultural reasons for overcoming the barriers between nonhuman and human species. However, because the claims encompass a mere aggregation of embryonic cells, this argument is not persuasive. Thus, as stated in the previous office action, "...other chimeras were known and there was a desire in the art to study development. Therefore, motivation existed at the time of invention to modify the teaching of Gustafson to include human/non-human primate aggregates".

In the response filed June 19, 2002 in paper no. 21, applicant argues that although Gustafson utilizes chimeras to study pregnancy retention and placental development, as per an embodiment of the present invention, the issues and discussion are very far from anything involving human biology. Applicant states that the present invention describes embryos produced for ES cells from two different primate species, one of which is human. Applicant argues that Gustafson is solidly with the scientific field of animal husbandry. Applicant argues that Gustafson would only motivate the ordinary artisan to apply the teachings therein to farm animals. Applicant argues that Gustafson would not motivate the ordinary artisan to make chimeras between species of non-domesticated animals such as primates. These arguments are not persuasive.

Applicant admits in the June 19, 2002 response that a study of pregnancy retention and placental development is an embodiment of the specification that is taught by Gustafson, although applicant seems to believe that Gustafson is only motivational for other farm/domesticated animals. However, human fertility, pregnancy, fetal development as well as placental biology/biochemistry are also areas of active research. The artisan reading Gustafson prior to the present invention would have realized that these types of studies could be performed using human/primate chimeric embryos.

Applicant also argues that Gustafson has been cited twice in the literature indexed in Science Citations Index since it was published. This argument is not persuasive.

The number of citations for any particular reference is not a statement for or against obviousness. The citation of Gustafson a few times does not lower its stature as prior art, as the frequency of reference to an article has no bearing on an obviousness rejection. The criterion for an

obviousness rejection is what the ordinary artisan reading Gustafson, at the time of the instant invention, would realize from the teachings and motivation of Gustafson.

Applicant also argues that the field of primate biology teaches away, for cultural and social reasons, from consideration of overcoming reproductive barriers between nonhuman species and humans. Applicant argues that the Examiner has not provided any reference that teaches or suggests chimeric embryos containing human cells. Applicant states that there was a teaching away of the formation of chimeric embryos containing human cells. For these reasons, applicant states that Gustafson lacked the motivation indicated by the office action and that it would not have been obvious to one of ordinary skill in the art to make a cell aggregate comprising human cells. These arguments are not persuasive.

A teaching away amounts to a teaching that something will not be operational. See *In re Gurley*, 27 F.3d 551, 553, 31 USPQ2d 1130, 1131 (Fed. Cir. 1994) ("[a] reference will teach away if it suggests that the line of development flowing from the reference's disclosures is unlikely to be productive of the result sought by applicant." Applicant has not provided any evidence to substantiate the allegations that social and cultural considerations concerning reproductive barriers between primates and humans teach that the claimed method would not be operational. Thus, for making a cell aggregation, Gustafson provides the appropriate teaching, suggestion and motivation.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The prior rejection of claims 39-43 and 55 stand, and newly added claim 85 is rejected under 35 U.S.C. 112, first paragraph, as failing to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention. The rejection is maintained for the reasons advanced on pages 13-14 of the prior Office action mailed 8/7/00 (Paper No.

17), and for the reasons advanced on pages 14-15 of the prior Office action mailed 10/29/99 (Paper No. 12). The aforementioned rejection is incorporated by reference.

Applicant argues that page 5 of the specification supports, literally, that the chimeric embryos can be propagated for varying periods of time in culture, and indicates that the claims have been amended to reflect this disclosure. See page 26 of Paper No. 20.

In response, it is acknowledged that claims 39-43 have been amended and claims 44-48 have been canceled. However, claims 39-43 have been amended to recite "where said embryonic cells develop cooperatively for no longer than 'x' days." It is maintained that the specification fails to disclose such embryos since the specification fails to support, explicitly, implicitly, or inherently, an embryo that has developed for up to 'x' amount of days. In the response filed June 19, 2002, applicant argues that the original specification states that the embryos can develop for varying periods of time and some embryos can be brought to term. Applicant argues that it was well known in the art at the time of filing that chimeric organisms may or may not cease to be viable at any given time. While applicant's statements are true as to the present disclosure and the knowledge in the art, such is not sufficient to provide evidence of possession at the time of filing for the very specific days now claimed: ten, twelve, fourteen, twenty-one and one hundred eighty days. Applicant has not pointed to any place in the specification where support for this language can be found. Claims amendments must have support in the specification as originally filed, and general disclosure or knowledge in the art cannot be substituted for specific support. Actual disclosure of the claimed days must be present in the specification.

With regard to claims 55 and 85, Applicant's arguments fail to address these claims. Accordingly, it is maintained that the specification lacks support for a resultant animal displaying a specific phenotype. Specifically, there is no recitation that the chimeric animal would be bipedal, have opposable thumbs, have the ability to reason, be able to communicate using sign language, or have the ability to communicate using speech.

Therefore, the specification as filed does not provide written description of the claimed invention and the noted limitations constitute new matter.

The prior rejection of claims 56 and 57 under 35 U.S.C. §112, first paragraph, as lacking written description, is moot in view of Applicant's cancellation of the claims.

Applicant's addition of claims 72-92 necessitates the new ground(s) of rejection as follows:

Claim 78 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 78 is directed to a chimeric embryo that contains fewer than fifty percent human cells.

The specification does not provide support for newly advanced claim 78 that requires that the embryo contain fewer than fifty percent human cells. The specification does not set forth any specific percentages with regard to the human/non-human primate cellular make-up of the disclosed chimeric embryos. The specification merely describes chimeric embryos in general terms and fails to mention specifically that the embryo would be comprised of fewer than 50% human cells. As such, the limitation "wherein said chimeric embryo contains fewer than fifty percent human cells" constitutes prohibited new matter.

Therefore, the instant specification does not provide written description of new claim 78.

Applicant's amendment to claims 10 and 13 requiring that the cells and chimeric animal be "immunologically tolerant" to cells from a human and from a non-human primate necessitated the new ground(s) of rejection under written description as follows:

Claims 10 and 13 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification does not provide support for claims 10 and 13 with newly advanced limitations directed to "immunologically tolerant". The specification fails to recite the limitation "immunologically tolerant" in any context. Furthermore, as is consistent with the prior rejection of the claims under written description (see subsequent rejection), the claimed human/non-human primate chimeric embryos are not described with regard to cellular contribution, and physical and anatomical structure. This renders the cell lines isolated there-from, and animals developed there-from, insufficiently described. Furthermore, cell lines and animals that must exhibit "immunologically tolerance", are not adequately described because there is no description within the specification that supports "immunologically tolerant" in the context of the claimed invention. As such, the limitations, "wherein said cell line is immunologically tolerant" and "wherein said chimeric animal is immunologically tolerant" constitute prohibited new matter. One skilled in the art would not conclude that the inventor had possession of an immunologically tolerant cell line or chimeric animal at the time the application was filed.

Claims 1, 3, 4, 6, 7, 10, 13, 28, 30, 31, 33, 34, 38-43, 50, 53, 55, and 59-71 stand, and newly added claims 72-92 are rejected under 35 U.S.C. 112, first paragraph, as failing to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention. The rejection is maintained for the reasons advanced on pages 15-17 of the prior Office action mailed 8/7/00, Paper No. 17. The aforementioned rejection is incorporated by reference.

Applicant argues that the literature teaches that species that are much more dissimilar than human and chimp or human and gorilla cooperate to produce a coherent organism, citing Fehilly et al., Meinecke-Tillman et al., Randi et al., and Takahata et al. Applicant argues that humans and chimpanzees are reproductively and developmentally similar, citing Gould et al., Strassmann, Soma, and Hobson. Applicant argues that the skilled artisan would fully expect that human/non-human primate embryo chimeras would have at least the same degree of multi-tissue chimerism and composite morphology as that reported for sheep and goat. See pages 28-29 of Paper No. 20. Applicant's arguments do not

address the lack of a written description of the currently claimed subject matter in the originally filed specification.

The claimed invention is directed to human/non-human primate chimeric embryos and animals developed there-from, and the specification fails to demonstrate possession of the invention by actual reduction to practice, clear depiction of the invention in a detailed drawing, or description with sufficient relevant identifying characteristics of the invention as a whole such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. It is maintained that the skilled artisan cannot envision the detailed structure of the claimed chimeric embryos with respect to human/non-human primate cellular contribution of the final product embryo, and thus, for these inventions, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method. One cannot describe what one has not conceived. See *Fiers v. Revel, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993).*

Therefore, it is maintained that the claimed invention does not meet the written description provision of 35 U.S.C. §112, first paragraph.

Claims 1, 3, 4, 6, 7, 10, 13, 28, 30, 31, 33, 34, 38-43, 50, 53, 55, and 59-71 stand, and newly added claims 72-92 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The rejection is maintained for the reasons advanced on pages 17-26 of the prior Office action mailed 8/7/00, Paper No. 17. The aforementioned rejection is herein incorporated by reference.

The Herbert Declaration filed under 37 CFR 1.132, February 7, 2001 attached to Paper No. 20 is not persuasive. The Herbert Declaration states that it would have been within routine skill at the time of filing to mix the human/non-human embryonic cells and follow standard protocols known in the art for mice, or for sheep/goat (this is the basis for the obviousness rejection of record). However, the Herbert

Declaration fails to show that such protocols could be extended to human/non-human primate embryonic cell culture. As the Declaration points out, "[g]enetics and other uncontrolled biological variability of organisms necessarily make outcomes unpredictable." Point #14, page 5 of the Declaration. It is necessary for the specification to teach one of skill in the art how to make and how to use the final product of the claimed invention, particularly in an unpredictable, and extremely undeveloped art, such as interspecies chimeric embryo/animal production and use. Further, one of the disclosed uses for such embryos falls within the field of another unpredictable art, xenotransplantation. While certain of the amended claims require immunological tolerance of the cells to the chimeric animal, the specification does not provide guidance as how one skilled in the art could overcome the rejection of tissues associated with xenotransplantation. With regard to the discussion of "how to use" the claimed chimeras as "model systems" for research, the model systems are not enabled by the specification because the specification fails to describe to one of skill in the art how to make and use the model system itself. See also reasons of record on page 21 of the prior Office action mailed 8/7/00 (Paper No. 17).

With regard to Applicant's arguments, it is initially noted that none of the 14 cited references were submitted (See Paper No. 20, attached PTO 1449) and that Applicant provided excerpts from three of those references in the Response. The Examiner cannot make a proper determination of the teachings of the prior art without evaluating the references in their entirety and as a whole. As stated in *Panduti Corporation v. Dennison Manufacturing Co.*, 774 F.2d 1082, 1093, 227 USPQ 337, 344 (Fed. Cir. 1985) "[t]he well established rule of law is that each prior art reference must be evaluated as an entirety, and that all of the prior art must be evaluated as a whole." However, in the interest of compact prosecution, the Examiner has attempted to address the excerpts provided by Applicant.

Specifically, Applicant cites excerpts of the references that they believe support embryo manipulation. However, the references fail to extend the techniques to a predictable final product embryo with regard to multi-tissue, cross-species chimerism such that there would be a reasonable expectation of success. Thus, none of the known techniques teach how to reproducibly obtain a

human/non-human primate chimeric embryo beyond the point of an embryonic cellular aggregate. In particular, Hammer pages 29-30 of Paper No. 20, appears to be developing mouse egg culture and manipulation techniques as a model for the culture and manipulation for mammalian eggs in general, and merely indicates that egg culture is fundamental and enabling in the context of egg manipulation and transgenesis. Hammer does not teach the generation of a cross-species chimeric embryo, even for the mouse, and therefore, fails to provide a reasonable expectation of success in the context of the generation of a cross-species chimeric human/non-human primate embryo. Likewise, Leoni, pages 30-31 of paper # 20, appears to be drawn to a technique for embryonic genome analysis, but fails to provide any evidence of interspecies chimeric embryos, and especially not human/primate chimeric embryo production, or the uses of such a chimeric embryo used in their methods of analysis. Applicant appears to argue that because the art of embryo manipulation is robust, the claimed invention is enabled. Even if one accepts that embryo manipulation is robust, the claimed invention is not to a method of embryo manipulation, but is instead directed to chimeric embryos themselves and animals derived there-from. It is this critical teaching, absent from Leoni, that is needed to support the enablement of the claimed invention.

Anderson (page 31 of the Amendment and Response) reports on manipulation of the mouse embryo and only discusses chimerism in the mouse system. As such, contrary to Applicant's assertion, this reference is not sufficient to provide evidence for transferability across species. The excerpt provided does not define from what species the chimeras were made. The production of same species chimeras is not the subject matter presently claimed or disclosed. There is no evidence that the subject matter of Anderson is interspecies chimerism.

Applicant also cites references to support chimerism within species (pages 31-32 of the Amendment and Response), however, none of these references teach cross species chimerism, and in view of the unpredictability as discussed above and in previous office actions, none of these references is sufficient to extend chimerism to human/non-human primate embryos.

Applicant cites references to support that primate embryos may be cultured. See page 32 of the Amendment and Response). However, none of these references provide a nexus between primate embryos and a human/non-human primate embryo. The ability to culture a primate embryo cannot be extrapolated to the ability to make and use a cross-species human/primate chimeric embryo.

Finally, Applicant contends that the existing art was sufficient at the time of filing to permit the ordinary artisan to construct chimeric embryos, cell lines, and animals of the present invention. See pages 32-33 of the Amendment and Response.

In response, it is maintained that the development of an inter-species chimera is completely unpredictable with respect to the resulting embryo, and with respect to its physical and anatomical structure. None of the cited references provide a reasonable correlation to extend the prior art embryonic culture techniques to the generation of a human/non-human primate embryo, particularly a resulting embryo having predictable characteristics. To this end, it is acknowledged that the skilled artisan would be able to follow standard, well known embryonic techniques to mix human embryonic cells with non-human primate embryonic cells to form cellular aggregates, however, it is maintained that it is not known under what conditions, if any, development would proceed to later embryonic developmental stages, particularly whether such an embryo would progress through development and result in a viable pregnancy. See, e.g. page 20 of the specification wherein Applicant states, "If developmental incompatibilities between chimpanzees and human blastomeres or ES cells can be experimentally overcome, these chimeric fetuses may eventually be brought to term," and "As barriers to developmental compatibility between chimpanzees and humans are surmounted..." (emphasis added). Clearly, this passage indicates that applicant had doubts as to the success of producing interspecies human/primate chimeric animals.

Applicant's amendment to claims 10 and 13 requiring that the cells and chimeric animal be "immunologically tolerant" to cells from a human and from a non-human primate necessitated the new ground(s) of rejection under enablement as follows:

The specification fails to teach how to make immunologically tolerant chimeric human/non-human primate tissues for use in xenotransplantation as taught by the disclosure. With regard to this limitation, Applicant discusses Gustafson et al., who teach skin grafts from sibling to chimera and report that 3 of the 4 chimeras tolerated the graft. See pages 17-18 of Paper No. 20. However, the specification specifically contemplates that the cells and tissues of the chimeras of the instant invention are useful as a source for transplantation (page 11), quite the opposite of the sibling to chimera paradigm exemplified in Gustafson. Neither the specification nor the prior art support that chimeric tissues comprised of cells from two different species would be "tolerated" by a recipient upon xenotransplantation, and, thus, the specification fails to provide an enabling disclosure for this limitation in the claims. Since the claimed human/non-human primate chimeric embryos are not taught or described with regard to cellular contribution, and physical and anatomical structure, it follows that transplantation of the cell lines isolated there-from, and animals developed there-from is not enabled. Cell lines and animals which must be "immunologically tolerant" are not enabled since there is no teaching or guidance within the specification which supports "immunologically tolerant" in the context of the "how to use" the chimeric embryos for xenotransplantation. Gustafson requires a chimeric animal as a donor, a product that is unpredictable as set forth in this record.

In summary, applicant's arguments do not overcome the art recognized unpredictabilities in the making and using of human/primate chimeric embryos or human/primate chimeric animals. As established in this record, the art taught at the time of filing that the production of interspecies chimeric embryos and interspecies chimeric animals was unpredictable. The specification does not provide guidance either in the form of instruction or working examples so that the skilled artisan would know how to overcome these unpredictabilities and make the claimed invention. Given the teachings in the art at the time of filing, the extent of experimentation would be undue as there would not be a reasonable expectation of success.

In the response of June 19, 2002 applicant states that U.S. Patents, and the references cited therein, 6,211,429 (Machaty) and 6,376,742 (Yanagimachi) support the enablement of the present claims. However, the examiner, in reviewing these two patents cannot find any teachings regarding the production of chimeric embryos where human embryonic cells were mixed with nonhuman primate embryonic cells. Indeed, neither the claims of Machaty nor the claims of Yanagimachi, if implemented, would ever lead to a chimeric embryo or a chimeric animal. In Machaty, the claims are directed to methods of oocyte activation and methods of nuclear transfer methods. Oocyte activation does not lead to any type of chimeric as there is no other haploid genome donor involved. Also, nuclear transfer would not lead to a chimeric, following the claims of Machaty as the genome transferred is from one mammal. Thus, in the methods of oocyte activation claims or the methods of nuclear transfer claims of Machaty, cells from two different species are never mixed as is required for the instant claims. In Yanagimachi, the claims are to methods of producing a transgenic mammal by sperm-mediated delivery of a DNA transgene to a fertilized egg. As in Machaty, the claims of Yanagimachi do not require the mixing of a cells from different species of mammals. Further, a review of the Machaty and Yanagimachi specifications indicates that neither contemplated the production of embryos or animals by the mixing of cells from different animal species. In other words, neither specification contemplates the production of a chimera as in applicant's claims and specification.

With regards to Machaty and Yanagimachi applicant argues that the disclosure of these patents, and the references disclosed therein, enable the culture of primate embryos, and cites Homa (1994), Herbert (1995) and Chan (2000). Copies of the Homa and Herbert references have not been submitted, and thus these references have not been considered. Applicant also argues that various methods are disclosed for fusing and/or cooperatively aggregating two cell types together and cites Prather (1996) and Prather (1991). Applicant argues that methods of foreign DNA transmission by ICSI were known and cites Bavister (1983). Applicant argues that the fertilization and cleavage of rhesus monkey oocytes was also known and cites Boatman (1987). Applicant argues that the in vitro growth of nonhuman primate

and pre and peri-implantation embryos was know and cites Bavister (1990). Applicant also argues that maturity at collection and the development potential of rhesus monkey oocytes was known and cites *Bio. Reprod.*, 42, 703-711. These arguments are not persuasive.

Many of these references have not been supplied with the response filed June 19, 2002, in paper no. 21, and the examiner cannot comment on their teachings and how such teachings do or do not support applicant's enablement arguments. Chan does provide for methods of culturing monkey (primate) embryos (page 27, cols. 1-2, bridg. Parag.). However, the enablement issue is not based on the unpredictability of methods for culturing primate chimeric embryos. Neither Prather reference discusses fusing cells or aggregating two cell types together. Prather (1991) discusses the cloning of domestic animals by splitting embryos and cloning. Prather (1996) similarly discusses only cloning methods for farm animals. These papers do not discuss methodology in common with applicant, as Prather (1991) disclose embryo splitting where a blastomere(s) of an embryo is inserted into a zona pellucida (Prather, 1991, page 208, parag. 3). Both Prather (1991) and Prather (1996) disclose cloning by nuclear transfer where a nucleus or cell is inserted into an enucleated oocytes. Neither Chan, Prather (1991), Prather (1996), Machaty nor Yanagimachi, disclose the formation of embryos by the aggregation of two different embryonic cell types as is required for the present claims. This art does not provide enablement support for applicant's claims because the methodology of Chan and each Prather reference is materially different from that needed to achieve applicant's invention.

Accordingly, for the reasons of record and for the reasons set forth above, the prior enablement rejection is maintained.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 3, 4, 6, 7, 10, 13, 28, 30, 31, 33, 34, 38-43, 50, 53, 55, and 59-71 stand, and newly added claims 72-92 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The prior rejection of the claims with respect to the claim recitation "chimeric embryo" is maintained for the reasons advanced on page 27 of the prior Office action mailed 8/7/00, Paper No. 17. Applicant provides no arguments with regard to this ground of rejection and only reiterates the Examiner's interpretation of the term to mean simply a mixture of cells from two individuals. See page 34 of Paper No. 20.

The prior rejection of claims 39-43, as it now applies to new claims 74, 91, and 92, with respect to the term "viable" is maintained for the reasons advanced on pages 27-28 of the prior Office action (Paper No. 17). Applicant's arguments appear to be directed to the limitation "viable" with respect to the description of the embryo being alive and not necessarily progressing through development and beyond term. See page 34 of Paper No. 20. However, it appears that Applicant's definition of the term "viable" with respect to the embryos is repugnant to the meaning supplied by the art. See page 28 of the prior Office action, Paper No. 17, wherein the Examiner sets forth the definition of viability from Stedman's Medical Dictionary. It is noted that a term in a claim may not be given a meaning repugnant to the usual meaning of that term. Any special meaning assigned to a term must be clear in the specification (*Multiform Dessicants Inc. v. Medzan Ltd.*, 133 F.2d 1473, 1477, 45 USPQ2d 1429, 1432 (Fed. Cir. 1998)). The specification as originally filed does not clearly provide a "specific meaning."

With regard to claim 13, and new claim 83, the prior rejection with respect to the term "derived" (in new claim 83) and "originating" (in newly amended claim 13), is maintained for the reasons advanced on page 27 of the prior Office action (Paper No. 17). Applicant indicates that their amendments overcome the rejection. However, the original rejection was set forth on the grounds that the metes and bounds of the term "derived" could not be deciphered since the term represents merely a starting source which would go through numerous changes and steps to attain the stopping point of "animal". To this end, amendment to the claim to recite "originating", similarly fails to overcome this ground(s) of rejection.

The prior rejection of claims 60-69, and new claims 79, 81, 82, and 86-88, as being indefinite for reciting statements of use having no material effect on the composition, is maintained for the reasons

advanced on page 28 of the prior Office action (Paper No. 17). Applicant's response fails to address this ground(s) of rejection.

Applicant's amendment to the claims to require that the embryonic cells "remain attached to one another and cooperate in the formation of a further developing embryo" or "develops cooperatively" necessitated the new ground(s) of rejection as follows:

Claims 1, 3, 4, 6, 7, 10, 13, 28, 30, 31, 33, 34, 38-43, 50, 53, 55, and 59-92 include the new claim limitation requiring the embryonic cells to "remain attached to one another and cooperate in the formation of a further developing embryo." This limitation is vague and indefinite with regard to what is intended to be encompassed within the metes and bounds of "cooperative embryonic development". Applicant's arguments appear to indicate that the starting point of aggregation is excluded from the limitation, and point to places within the specification for support for the newly added limitation. See page 22 of Paper No. 20. However, the specification, in fact, sets forth that "aggregation" is encompassed within the metes and bounds of the limitation. See specification at page 1, lines 17-19, and page 16, line 3, and page 18, line 21. As such, it is unclear what is encompassed within the claim limitation. While the claims include a limitation which may require carrying out steps of development of an embryo beyond the step of aggregation, given their broadest reasonable interpretation in light of and consistent with the specification, the claims encompass the starting point of the development of an embryo, *i.e.*, aggregation of the embryonic cells, and not necessarily any point beyond aggregation. As such, the claims are interpreted to encompass mere "aggregation" of the cells to describe the starting point of "cooperative" development of an embryo since the specification appears to support that "cooperative development" encompasses "aggregation" of the embryonic cells.

Applicant's amendment to claim 10 to require that a cell line isolated from a chimeric embryo comprising cells ... embryonic ...totipotent necessitated the new ground(s) of rejection as follows:

Claim 10 is confusing as to whether it is the cell line or the chimeric embryo that is comprised of embryonic cells, blastomere cells, blastocyst cells, undifferentiated immortal cells, pluripotent cells or totipotent cells.

Applicant's amendment to claims 10 and 13 requiring that the cells and chimeric animal be "immunologically tolerant" to cells from a human and from a non-human primate necessitated the new ground(s) of rejection as follows:

In claim 10 and 13, the limitation "immunologically tolerant" renders the claims vague and indefinite with regard to what is intended to be encompassed in the metes and bounds of immunological tolerance exhibited by a cell line or by an animal. In particular, the specification fails to provide a standard for measuring immunological tolerance of chimeric human/non-human primate tissues when transplanted as is consistent with the disclosure's use. With regard to this limitation, Applicant's arguments seem to rely on the standard set forth in Gustafson et al. (*supra*), who teach skin grafts from sibling to chimera and report that 3 of the 4 chimeras tolerated the graft. The specification specifically contemplates that the cells and tissues of the chimeras of the instant invention are useful as a source for transplantation (page 11), quite the opposite of the sibling to chimera paradigm. To this end, neither the specification nor the prior art support that chimeric tissues comprised of cells from two different species would be tolerated by recipient upon transplantation, and, thus, it is unclear to what standard the new limitation "immunologically tolerant" pertains. Furthermore, it is completely unclear how *in vivo* tolerance of grafts describes the immunological tolerance present in an isolated cell line as recited in claim 10. Tolerance describes a concept involving an intact immune system, not an isolated cell line. Gustafson uses the concept "immunologically tolerant" as the non-rejection of a cell by an animal's immune system for a period of time. Thus, "immunologically tolerant" would appear to describe an intended use of a cell and not the cell itself. Clarification and/or amendment to the claims is requested.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title.

Claims 1, 3, 4, 6, 7, 13, 28, 30, 31, 33, 34, 39-43, 59-67 and 69-71 are rejected again 35 U.S.C. 101 for the reasons of record, and newly presented claims 72-83 and 86-92 are rejected under 35 U.S.C. 101 for the same reasons. Applicant argues that (a) the claims do not include a human being and (b) the USPTO cannot refuse to issue a patent covering a human being.

A. Response to arguments that the claims do not include a human:

Applicant argues that the claimed subject matter is not a human being but rather man-made chimeric embryos and animals developing from them. Response at page 11. In Applicant's view, embryos that do not contain exclusively human cells, are not human, Response at page 12, and animals containing human cells are not human beings, Response at page 13. According to Applicant, "a proportion of human cells in an organism do not make that organism a human being." Response at page 13. Applicant's arguments have been carefully considered but they are not persuasive.

In the second response, Paper No. 15, Applicant agreed that "the claimed invention is not limited to a specific degree or range of chimerism." The Starzl et al. publication reports on human beings who received primate organ transplants and became chimeric as a result. The examiner discussed this paper in the third Office action, Paper No. 17. Starzl et al. report that grafted leukocytes migrated throughout the body and the human patients became "chimeras," made by human intervention, comprising human and non-human cells. The patients were not converted to non-human status by engraftment of the non-human cells. Similarly, the claimed embryos and chimeras are not converted to non-human status merely because they include some non-human cells. A proportion of non-human cells do not negate the human's status as a human, nor does alteration by human intervention.

Independent claims 1, 28, 77 and 79 are directed to chimeric embryos. The claimed embryos comprise human embryonic cells and embryonic cells from one or more non-human primates. Independent claims 13 and 83 are directed to chimeric animals "originating from" and "derived from" chimeric embryos comprising human embryonic cells and embryonic cells from one or more non-human primates. The claims do not state any limitation on the relative proportions of human and non-human

cells in the embryo or animal. Thus, the claims include any proportional mixture of the human and non-human cells.

The broadest reasonable interpretation of the claims when read in view of the specification is that they include a human. The written description advises that "[t]he invention comprises, in part, human embryos," and that the human cells and non-human cells contained in the chimeric embryo are composed of "any number of cell types," page 16. The ordinary dictionary meaning of human embryo is "the developing human individual from the time of implantation to the eighth week after conception." See, e.g., Merriam Webster Medical Dictionary, 1993 (copy attached). Claim 43 describes embryo cell cooperation up to 180 days, thus using the word embryo to describe the developing chimeric embryo beyond 22 weeks, and without limiting the claim to that time period. Thus, Applicant is using the term "embryo" more broadly than the ordinary dictionary sense that describes development up to eight weeks.

The usefulness of the invention is said to relate to features described as "human." E.g., "[t]he present invention is an invaluable model in the study [of] the effects of various stimuli on human heart tissue," specification, page 10, and "[o]nly by studying the actual development of human tissues and organs can we understand the disorders that affect human development . . .," page 13. The invention is said to provide a source for "human tissue and ultimately human organs," page 14. It is reasonable to conclude that the claims include a human because they do not provide limitations that distinguish the claims from a human.

Claim differentiation provides an independent basis for concluding that the claims include humans. The "chimeric embryo" of claim 1 is reasonably construed to include a human embryo because the sole difference between claim 1 and dependent claim 38 is that claim 38's embryo is "non-human." Independent claims 28, 77 and 79 use the same "chimeric embryo" term as used in claim 1. When the same term is used in different claims, it is reasonable to interpret it in the same way. Thus, claims 28, 77 and 79, and their dependent claims, include a human. Like claim 1, claims 13 and 83 are reasonably construed to include a human because the sole distinction between them and dependent claims 53 and

55, and claims 84 and 85, respectively, is that the dependent claims recite the single further limitation "wherein said animal [or chimeric animal] is non-human."

B. Response to arguments that there is no statutory authority for this rejection

Applicant argues that: (1) the Director "has no authority to reject the claims . . . on the grounds that they 'embrace a human being,'" Response at page 11; (2) "[n]owhere does the statute restrict patentability based upon embracing a human being," Id.; (3) "neither courts nor the Patent Office are authorized to embellish the statutory requirements for patentability," Id.; and (4) "[w]hether or not the PTO believes Congress intended to bar patentability of inventions that embrace a human being is not the issue . . . the PTO has no authority to fill the gap," Response at page 12. The arguments have been carefully considered but they are not persuasive.

Ordinary canons of statutory construction support the interpretation of patentable subject matter that the prior office actions advanced. Statutory words in the first instance must "be interpreted as taking their ordinary, contemporary, common meaning." *Perrin v. U.S.*, 444 U.S. 37, 42 (1979). As the Supreme Court stated prior to the passage of § 101, "legislation when not expressed in technical terms is addressed to the common run of men and is therefore to be understood according to the sense of the thing, as the ordinary man has a right to rely on ordinary words addressed to him." *Addison, et al. v. Holly Hill Fruit Products, Inc.*, 322 U.S. 607, 617-18 (1944). Despite the breadth of these terms, recognized in *Diamond v. Chakrabarty*, 447 U.S. 303, 308 (1980), the terms "manufacture" or "composition of matter" would not have been regarded in ordinary parlance when § 101 was passed as possibly reflecting a Congressional intent to encompass human beings. Rather, these terms, in their ordinary common meaning, would have been regarded contemporaneously as referring to items other than humans that can be possessed, introduced into commerce, and made the subject of trade. *Cf. Kewanee Oil Co. v. Bicron Corp.*, 416 U.S. 470, 480 (1973) ("The productive effort thereby fostered will have a positive effect on society through the introduction of new products and processes of manufacture into the economy, and the emanations by way of increased employment and better lives for our

citizens.") In contrast, humans are the beings for whose sake such new products or methods of manufacture would be introduced.

This construction is not contradicted by the legislative history of the Patent Act. As the Supreme Court noted in Chakrabarty, the Committee Reports accompanying the 1952 Act reflect an intent to mandate a broad scope for patentable subject matter to "include anything under the sun that is made by man." S.Rep.No.1979, 82d Cong., 2d Sess., 5 (1952); H.R.Rep.No.1923, 82d Cong., 2d Sess., 6 (1952). These statements too, however, do not reach so far as to include human beings within patentable subject matter. Rather, like the terms of the statute itself, they presume a dichotomy between man and those inventions and discoveries that could be made by man.

The American rule that statutes are to be construed to avoid Constitutional issues also applies to this question. It has long been an axiom that "where an otherwise acceptable construction of a statute would raise serious constitutional problems, the court will construe the statute to avoid such problems unless such construction is plainly contrary to the intent of Congress." *Edward J. DeBartolo Corp. v. Florida Gulf Coast Building & Construction Trades Council*, 485 U.S. 568, 575 (1988). In a public policy statement and testimony to Congress made fifteen years ago, the USPTO made it clear that it would not interpret statutory subject matter to encompass humans because the exclusionary rights conveyed by a patent would be difficult at best to apply to humans in view of the constitutional rights of human persons. "Animals – Patentability", 1077 Off. Gaz. 24 (April 21, 1987); "Patents and the Constitution: Transgenic Animals: Hearings Before the Subcommittee on Courts, Civil Liberties, and the Administration of Justice of the Committee on the Judiciary," House of Representatives, 100th Cong. 1st Sess. (June 11, July 22, August 21, and November 5, 1987). The rule directing that ambiguous statutory language be construed not to give rise to Constitutional questions is a direction that certain kinds of questions are a matter for the legislature to address in the first instance.

"The grant to the inventor of the special privilege of a patent monopoly carries out a public policy adopted by the Constitution and laws of the United States, 'to promote the Progress of Science and useful Arts, by securing for limited Times to . . . Inventors the exclusive Right . . .' to their 'new and

useful' inventions. *United States Constitution, Art. I, s. 8, cl. 8.*" *Morton Salt Co. v. G.S. Suppiger Co.*, 314 U.S. 488, 492 (1942). Long before the term "useful" was incorporated in current § 101, "useful" as used in the patent context had been construed to include the connotation that an asserted invention "should not be frivolous, or injurious to the well-being, good policy, or good morals of society." *Tol-O-Matic, Inc. v. Proma Produkt-Und Marketing Gesellschaft m.b.H.*, 945 F.2d 1546, 1552-53 (Fed. Cir. 1991), *citing, inter alia, Lowell v. Lewis*, 15 F.Cas. 1018 (C.C.Mass. 1817) (Story, J.). Public policy takes into account the common sense of the community, issues that are controversial by nature, and issues that tend to be injurious to the public or contrary to public good. Black's Law Dictionary 1231 (6th ed. 1990). The question of whether humans should be the subject of exclusive patent rights raises grave issues going to the core of what a "useful" invention is.

When Congress included the term "useful" in the statute, the requirement that an invention not be frivolous, or injurious to the well-being, good policy, or good morals of society was incorporated with it because Congress did not disavow any of these limitations. *Cf. Lorillard v. Pons*, 434 U.S. 575, 580-81 (1978) ("where, as here, Congress adopts a new law incorporating sections of a prior law, Congress normally can be presumed to have had knowledge of the interpretation given to the incorporated law, at least insofar as it affects the new statute."). "It is the public interest which is dominant in the patent system." *Mercoid Corp. v. Mid-Continent Inv. Co.*, 320 U.S. 661, 665 (1944). However, both the Office and its reviewing court have recognized that this doctrine must be applied so as not to displace the police powers of the states or other federal agencies. *Ex Parte Murphy*, 200 USPQ 801, 803 (Bd. Pat. App. & Int. 1977); *Juicy Whip, Inc. v. Orange Bang, Inc.*, 185 F.3d 1364, 1366, 51 USPQ2d 1700, 1702 (Fed. Cir. 1999).

Concerns for deference to the powers of other institutions of government weigh in favor of considering the patenting of humans as the kind of invention that would not be considered "useful" under the doctrine of *Lowell v. Lewis*. It is essential that the USPTO not, by granting patents before the people's representatives have spoken, usurp the power of Congress to speak first to these issues. The discretion to consider the well-being and good policy of society implicit in the statutory term "useful" is

properly applied when a refusal to grant a patent is necessary to avoid preempting the power of Congress to define essential questions of public policy. This principle is all the more applicable in the current context, since Congress has long understood that the USPTO would decline to issue patents covering such subject matter and thus would have good reason to regard itself as having been preempted if the USPTO were instead to issue such patents. Contrary to applicant's argument, given this history, the USPTO would be acting improperly in the place of Congress to "fill a gap" in the law if it were to grant a patent covering human beings; it acts pursuant to soundly based deference to the constitutionally empowered institutions of government in denying such a patent application.

Moreover, it is well established that judicial deference to such an agency interpretation is "particularly appropriate where, as here, an agency's interpretation involves issues of considerable public controversy, and Congress has not acted to correct any misperception of its statutory objectives." *United States v. Rutherford*, 442 U.S. 544, 554 (1979). Congress amended Title 35 several times since the PTO's pronouncements on these issues in 1987. It could have acted to correct any misperception, but took no steps to do so. Indeed, the Supreme Court in *J.E.M. AG Supply v. Pioneer Hi-Bred Int'l*, 534 U.S. 124 (2001), in declining to exclude plants from patent eligibility, relied on the fact that, in the sixteen years after the USPTO's "highly visible" decision to issue utility patents for plants, Congress "failed to pass legislation indicating that it disagrees with the PTO's interpretation of § 101". Just as Congress's acquiescence in the USPTO's announced views on the patentability of plants weighed in favor of the Court's finding plants eligible for utility patents, Congress's acquiescence in the USPTO's announced views on the non-patentability of humans weighs in favor of finding humans not eligible for patents.

Applicant repeats the argument that other patents have issued on animals comprising human cells and that Applicant's invention should be patented under the same standard. The examiner responded to this argument in the second Office action, Paper No. 12, page 8. While the examiner is of the view that the same standard under 35 U.S.C. 101 is being applied in this case as in others, patentability is determined on the totality of the record on a case-by-case basis. Whether similar claims in other applications may have been treated differently is neither controlling nor dispositive on how they are

to be treated in any other application. *In re Wertheim*, 541 F.2d 257, 264, 191 USPQ 90, 97 (CCPA 1976).

Claims 1, 3, 4, 6, 7, 10, 13, 28, 30, 31, 33, 34, 38, 39-43, 50, 53, 55 and 59-92 are rejected under 35 U.S.C. § 101 because the claimed invention is not supported by either a specific, substantial or credible asserted utility or a well established utility.

Applicant's disclosure asserts several utilities for the claimed compositions. These utilities are summarized on page 14 of the specification and encompass use of the chimeras for: (1) developmental toxicology assays; (2) studies of embryonic developmental disorders; (3) cryopreservation for future use; (4) studies in cardiovascular physiology; (5) sources of bone marrow for transplantation; (6) source of hearts for transplantation; (7) sources of tissue for skin grafts; (8) source of organs for transplantation; (9) model system for use in research; and (10) model system for use in clinical trials.

Applicant's claims can be divided into two general categories of invention. The first category are claims directed to an embryonic stage of development where the claims do not require that the embryonic chimeras have developed to the stage of producing organs or specific tissue. These claims are 1, 3, 4, 6, 7, 10, 28, 30, 31, 33, 34, 38-43, 50, 59, 60, 62, 72, 73-80, 91 and 92. The second category is claims that require that the embryonic chimera has developed to produce a specific tissue, organ, or animal. These claims are 13, 53, 55, 61, 63-71 and 81-90.

Utilities (4)-(10) recited above are only applicable to the second category of claims, while utilities (1)-(3) above are mostly applicable to the first category of claims, but may potentially be applicable to the second category as well.

Utilities (1)-(3) are not specific or substantial utilities. A specific utility is one that is not general to a broad class of the invention. Developmental toxicology assays, studies of embryonic developmental disorders and cryopreservation for future use in research are all general utilities that would be applicable to any embryonic cell or human embryonic cell. Applicant's disclosure fails to provide any specific utility of the claimed invention that would not generally apply to all embryos. Thus, asserted utilities (1)-(3) are not specific.

Utilities (1)-(3) are also not substantial. A substantial utility is one that defines a "real world" use. Utilities that require or constitute carrying out further research to identify or reasonably confirm a "real world" use are not substantial utilities. Utilities (1)-(3) are all directed to utilities that are directed to studying the properties of the claimed embryonic chimera itself or the mechanisms by which the chimera develops. Thus, asserted utilities (1)-(3) are not substantial.

Finally, none of utilities (4)-(10) are credible. Utilities (4)-(10) each require the development of the human/non-human primate chimera to a stage that produces a specific tissue, organ, or animal. As of the filing date of the application, and even currently, development of specific tissues, organs or animals from embryonic cells is not credible. Pennisi et al. (Science, Vol. 288, 9 June 2000) and Westhusin et al. (Theriogenology, Vol. 55, 2001) each indicate that there are considerable differences in the success of growing cloned embryos from different species. While the cloning methodology has met success in a variety of different species mammals, the tools, details and "tricks of the trade" have differed for almost all species (see Pennisi et al., page 1722, column 3, page 1726, and page 1727, columns 1 and 2; and Westhusin et al., abstract, paragraph bridging pages 36-37, last paragraph page 40, and last two paragraphs of page 41.) These references clearly establish that even within more developed techniques for embryo manipulation, such as cloning, the species and methodology are important in gaining success. This invention, however, did not involve a methodology as well developed as cloning, but instead allegedly utilizes chimerism to produce specific tissues, organs and animal chimeras. However, in November of 1998, almost a year after the filing of this application, Gearhart, a well respected embryonic stem cell researcher, is referenced as indicating that the production of human chimera utilizing stem cell research is "an even greater shot in the dark than cloning." Tenenbaum, Dave, http://whyfiles.org/shorties/stem_cell.html. Thus, it is clear from the post-filing art that at the time of filing, the production of a human/non-human primate chimera that can produce specific tissue, organs or an animal chimera was not credible.

As is often quoted, "A patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion." *Brenner v. Manson,* 383 U.S. 519, 536, 148 USPQ 689, 696.

Therefore, for the reasons set forth above, the claimed invention lacks a specific, substantial and credible utility.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deborah Crouch, Ph.D. whose telephone number is 703-308-1126. The examiner can normally be reached on M-The, 8:30 AM to 7:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah J. Reynolds can be reached on 703-305-4051. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Deborah Crouch

DEBORAH CROUCH
PRIMARY EXAMINER
GROUP ~~1800~~ 1630

dc
January 28, 2003